A Drug Response Predictor (DRP®) is associated with enhanced Overall Survival in the phase 2 trial in advanced, recurrent ovarian cancer patients treated twice daily with 2X-121/Stenoparib (NCT03878849)

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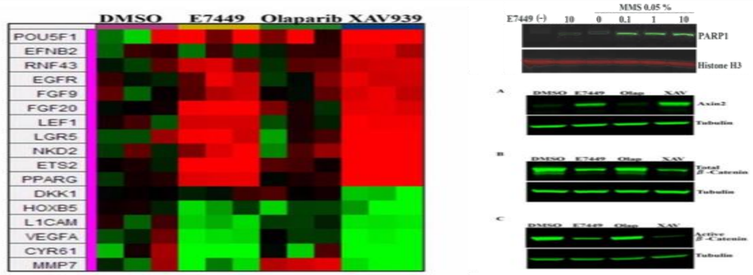
Abstract

2X-121 (stenoparib/ E7499) inhibits PARP1/2 (1nM ~IC50) and Tankyrase 1/2 (IC50 ~50nm). As such, 2X-121 impairs DNA repair while simultaneously inhibiting the WNT/ß-catenin oncogenic signaling pathway. A Drug Response Predictor (DRP®) specific for 2X-121 has been developed from the *in vitro* sensitivity of cell lines in monolayer culture and highlights the gene expression profiles correlated with sensitivity to 2X-121. This DRP® signature is comprised of 414 genes, many of which reflect WNT/ ß-catenin pathway activity.

In a phase 1 dose escalation clinical study, 2X-121 showed clinical responses, especially in ovarian cancer patients. The 2X-121 DRP® retrospectively was able to identify patients who were most likely to benefit from 2X-121. A follow-on, open label phase 2 trial in 3L+ ovarian cancer patients with a DRP score > 50 started May 2023 with 2X-121 dosed BID for the first time. A total of fifteen (15) patients were enrolled independent of BRCA or Homologous DNA Repair status. Most patients were heavily pre-treated. Prior treatment included PARP inhibitors, mirvetuximab soravtansine and immunotherapy. Fourteen patients had platinum resistant disease, one had primary platinum refractory disease. The data show durable clinical benefit in patients with varied genetic and treatment backgrounds. Two patients (one BRCAmut and one BRCAWT) remained on therapy for 27 months. Additionally, one patient previously treated with PARP inhibitors showed a complete, confirmed response and remained on treatment > 10 months. Kaplan-Meier analyses show that the median Overall Survival is 22 months. Importantly, 2X-121 was well tolerated and did not show the myelotoxicity typical of earlier PARP inhibitors.

We assessed whether the DRP score from pre-treatment biopsies might be related to enhanced Overall Survival. Indeed, patients with higher DRP scores reliably showed the greatest OS. In a continuous cox proportional hazard analysis, a 50-point difference in DRP score was associated with a hazard ratio of 0.1 (95% CI 0.0-3.2). Applying a fixed cutoff of 80 resulted in a hazard ratio of 0.13 (95% CI 0.02-0.9). To address the possibility that the DRP was prognostic rather than predictive, we assessed RNA expression data from biopsies in the public TCGA dataset of 481 high grade serous ovarian cancer treated with platinum and a taxane. The DRP scores ranged from 0 to 100 in the TCGA cohort. The 2X-121 DRP® did not identify patients with better OS (continuous cox HR=0.76 (95% CI 0.54-1.1)). Among 90 platinum resistant patients the hazard ratio was 0.96 (95% CI 0.39-2.3)

2X-121: a Dual PARP and Wnt Pathway Inhibitor



Left Panel shows gene expression profiles for 2X-121/ E7449 compared to DMSO control, the PARP inhibitor Olaparib and the Tankyrase inhibitor XAV939. The Right Panel Top shows PARP trapping by 2X-121/ E7499. The remaining three panels on the right show western blots for WNT pathway components – Axin and Beta catenin. Data from McGonigle et al., 2016

NCT03878849 Trial Specifics

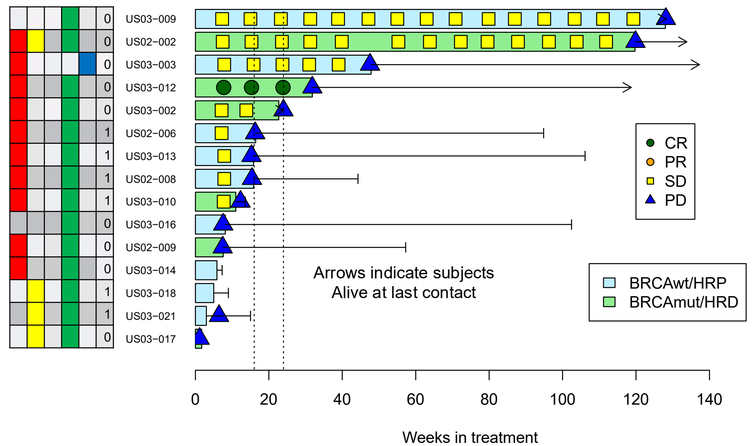
PhII Open-Label Clinical Study to Evaluate Stenoparib/2X-121 Monotherapy BID in Advanced, Recurrent Ovarian Cancer (NCT03878849)

Key Inclusion Criteria:
- Histologically or cytologically documented epithelial ovarian carcinoma
  - High grade serous, endometrioid, clear cell, carcinosarcoma, undifferentiated, and mixed histological subtypes
- Independent of platinum response, Platinum- free interval ≥ months
- Independent of BRCA/HRD status
- 2 or more previous chemotherapies/antibody therapies including treatment with other PARPi
- DRP > 50 on patient tumor biopsy for enrollment

Dosing: Stenoparib/2X-121 PO BID (200mg + 400 mg) until progression
Primary Objective:
- Objective Response Rate by RECIST v 1.1

Secondary Objectives:
- Clinical Benefit Rate at 16 weeks (CR+PR+SD)
- PFS, DoR, OS, Clinical benefit correlation with DRP score, QoL

Extended Clinical Benefit in BRCAwt and BRCAmut



Swimmer's Plot for the BID Cohort of NCT03878849. Each bar represents a single patient across time from first dose. Patient platinum status, key prior therapies are shown on the grid to the left. Note: 14 of the 15 enrolled patients were platinum resistant. The remaining patient was Primary platinum refractory. Arrows represent survival of patients.

References
Sharon McGonicle et al: E7449: A dual inhibitor of PARP1/2 and tankyrase1/2 inhibits growth of DNA repair deficient tumors and antagonizes Wnt signaling. Oncotarget. 2015 Dec 1;6(38):41307-23
Ruth Plummer et al: First-in-human study of the PARP/tankyrase inhibitor E7449 in patients with advanced solid tumors and evaluation of a novel drug-response predictor. British Journal of Cancer (2020) 123:525–533

New Protocol *Now Enrolling* PROC patients

Stenoparib Monotherapy in Platinum Resistant or Ineligible Ovarian Cancer

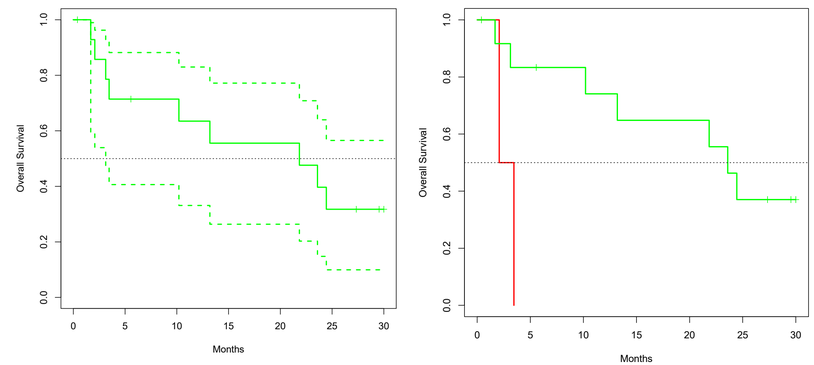
Objective: Solidify Dose for Pivotal Trial, Establish Cut-point for DRP Pre-selection in Pivotal Trial

Patients with Platinum Resistant or Platinum Ineligible Disease
- No more than 1L of chemo beyond declaration of Platinum Resistance, except ADCs
- No Platinum Refractory Pts or Pts with Ascites
- BRCA mutant and BRCAwt patients accepted

No DRP pre-selection- DRP will be assessed retrospectively in newer biopsy tissues
Randomization to one of two BID dose cohorts to address FDA's Project Optimus
- 200mg + 400mg (n=20) or 400mg + 400mg (n=20)

Safety and Efficacy
- Response Rate by RECIST v1.1, Clinical Benefit Rate, Progression Free Survival, Overall Survival

Overall Survival — OS by DRP test result



Kaplan-Meier Survival Analyses. Median Overall Survival (mOS) is 22 months in NCT03878849 (left panel, confidence intervals represented by the dotted lines). Right panel shows overall survival by DRP test results based on a pre-treatment biopsy: red is below DRP score 80 (N=2), green is above DRP score 80 (N=13). The hazard ratio is 0.13 (95% CI 0.02-0.9). A similar hazard ratio was observed in Phase 1 (Plummer et al, 2020)

Conclusions

1. **2X-121 shows extended clinical benefit with 2 patients on therapy more than 27 mos**
2. **Median Overall Survival = 22 months**
3. **The Stenoparib-DRP may be useful in identifying patients with greatest clinical benefit, particularly OS.**
4. **2X-121 has a unique, dual mechanism of therapeutic action**
5. **A new Protocol in PROC is now enrolling to explore 2X-121 more deeply**

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